IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Monty Krieger and Susan L. Acton

Serial No.:	08/765,108	Group Art Unit:	1646
Filed:	March 27, 1997	Examiner:	J. Ulm

For: *CLASS BI AND CI SCAVENGER RECEPTORS*

Assistant Commissioner for Patents
Washington, D.C. 20231

REPLY TO EXAMINER'S ANSWER

Sir:

This is a reply to the Examiner's Answer mailed May 17, 1999, to the Appeal Brief filed in response to the final rejection of claims 9-15, 19-22, and 44-50 in the Office Action mailed March 19, 1998 and maintained in the Advisory Action mailed August 3, 1998 in the above-identified patent application. It is believed that no fee is required with this submission. However, the Commissioner is hereby authorized to charge any additional required fees to Deposit Account No. 01-2507.

(1) SUPPLEMENTAL ARGUMENTS

The Board's attention is drawn to the Appeal Brief for a discussion of the claimed subject matter and why the claims are enabled. Only responses to those points made in the Examiner's Answer are discussed below.

a. Claims 11-13, 17, 19-22 and 44-50 are Enabled Under 35 U.S.C. § 112, first paragraph.

Claims 11-13, 17, 19-22, and 44-50 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the production of "an isolated nucleic acid encoding a scavenger receptor protein lacking one of the amino acid sequences that are disclosed in SEQ ID NOs: 4, 6, and 8" allegedly lacked enablement (Examiner's Answer page 3).

The Examiner's argument is based on the following:

(1) The term "binding activity identified above" in the specification is unclear.

(2) The claims allegedly encompass any protein capable of binding low density lipoproteins.

(3) Claim 11 allegedly places no structural limitation on the molecules and is therefore, a single means claim.

(4) Appellants could not rationally design the proteins encompassed by the claims.

"Binding activity identified above" is definite.

The portion of the specification that the Examiner is referring to is on page 38:line 38 to page 39:line 10. It is not clear why the Examiner is in fact referring to the specification because the *claims define the requisite binding activity.* The claimed "binding activity" is definite. The claims require the protein encoded by the nucleic acid molecule, which must hybridize to SEQ ID Nos 3 and 7, selectively bind to both low density lipoprotein and acetylated low density lipoprotein. There are numerous references in the application to the unique binding characteristics of the claimed SR-B1 proteins. For example, "haSR-BI differs from CD36 and

other modified lipoprotein receptors described to date in that its binding of AcLDL (acetylated low denisty lipoprotein) is inhibited by native LDL. SR-BI also binds HDL (high density lipoprotein) and mediates uptake of lipid from HDL into the cell." (page 10:line 37 to page 11:line 5). Another recitation of the binding properties of SR-B1 is

> The ligand binding specificities of CD36 and SR-BI, determined by competition assays, are similar, but not identical: both bind modified proteins (acetylated LDL, maleylated BSA), but not the broad array of other polyanions (e.g. fucoidin, polyinosinic acid, polyguanosinic acid) which are ligands of the class A receptors. SR-BI displays high affinity and saturable binding of HDL which is not accompanied by cellular degradation of the HDL. HDL inhibits binding of AcLDL to CD36, suggesting that it binds HDL, similarly to SR-BI. Native LDL, which does not compete for the binding of acetylated LDL to either class A receptors, CD36 or Var-261 cells, unexpectedly competes for binding to SR-BI. SR-BI and CD36 therefore define a second class of scavenger receptors, designated class B, which are referred to as members of the CD36 family which can bind to modified LDL. The ability of other known members of the CD36 family to bind to modified LDLs has not been reported.
>
> (Specification at page 11:lines 16-35).

Not only is it clear what the phrase "binding activity" refers to, it is also clear how to assay for that binding activity. There are numerous discussions and descriptions which would enable one of skill in the art to determine the binding activity of isolated SR-B1 proteins. For example, on page 16 there is a section entitled, "^{125}I AcLDL Binding, Uptake and Degradation Assays" that describes how to assay binding of AcLDL to protein. There are other sections entitled "HDL Binding Studies" (page 19) describing how to test for HDL binding to protein and

"Phospholipid Binding and Competition Assays" describing how to assay binding of lipoproteins and modified lipoproteins to protein.

The claims do not encompass any protein capable of binding low density lipoprotein: the claims are not single means claims.

Claim 11 is drawn to an isolated nucleic acid molecule

a. encoding a scavenger receptor protein type BI

b. that selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein,

c. that hybridizes to SEQ ID Nos. 3 and 7.

Clearly this claim does not encompass "any protein capable of binding low density lipoproteins."

The structure of SR-BI can be seen schematically, and contrasted with the structures of numerous other scavenger receptor proteins, by reference to Figures 1A and 1B. It is relatively routine to enter the data describing either a nucleotide sequence, or the amino acid sequence encoded thereby, and determine the physical structure. It is also readily apparent that SR-BI has a structure quite unique from that of the other known scavenger receptor proteins.

Moreover, contrary to the Examiner's assertion, the requirement for hybridization does place structural limitations on the claimed molecule. The application clearly describes how to perform hybridization assays so that discrimination occurs between members of different families within the CD-36 superfamily of proteins. It is true that hybridization experiments can

be done to produce absurd results, but when performed by one of ordinary skill in the art as outlined in the application there is no absurdity in their application or in the results of their application. (Please see pages 16 and 17 of the Appeal Brief mailed on February 11, 1999 ("Appeal Brief") and page 18: line 27 to page 19: line 6 of the application).

The binding activity requirement is discussed above.

In summary, the claimed molecules are defined in terms of structure, both gross structure as well as sequence structure, and in terms of function.

The Standard is not whether or not the Appellants can rationally design a protein.

The standard for whether a disclosure is enabling is whether one of skill in the art can make or use the claimed molecules without undue experimentation. It is not whether the "appellants can rationally design a nucleic acid encoding a functional scavenger protein having other than a natural amino acid sequence." As discussed in the Appeal Brief, the standard is one of undue experimentation where unpredictability is one of the factors to be considered. Contrary to the interpretation of unpredictability by the Examiner, this factor does not exclude the use of experimentation (see discussion of *In re Vaeck* in the Appeal Brief at page 23 to 24). What must be predictable are the tools and knowledge available to the skilled artisan at the time one attempts to make and use the claimed molecules. Thus, the present application must have enabled one of skill in the art as of the time it was filed to make proteins in a predictable manner, based on for example, which amino acid substitutions are considered conserved, i.e. an alanine to a glycine substitution, which amino acid substitutions are likely to create a non-functional

protein, i.e. the substitution of a glutamine with a glutamic acid, how to make the claimed molecules, and how to assay the claimed molecules for activity, i.e. using the binding assays discussed above. Thus, Appellants are not advocating a "make and test" standard which is based on a random making and testing of molecules as asserted by the Examiner. Rather, Appellants take the position that the skill in the relevant art was high in 1994, the priority date of the present application, and that one of skill in the art would not be limited to making random mutations and testing these for activity, but would use his knowledge (for example, based on the knowledge of which amino acids are substantially equivalent, and which amino acids are, or are not, conserved between species) to make informed choices of which molecules would likely be within the claims, and the experimentation to determine which change yielded useful molecules, would not be undue.

Appellants **have relied** upon the decisions of *In re Fisher, Amgen Inc. v. Chugai*, and *In re Wands* in their Appeal Brief. Appellants **are** applying the standards outlined in these decisions. These decisions are unequivocal in stating that it is the skill of the art at the time the application is filed that is relevant to the question of enablement. *In re Fisher* dealt with amino acids and the breadth of claims drawn to peptides, but *In re Fisher* was based on technology that was "state of the art" before the world even knew what the structure of DNA or the genetic code was. The standard of *In re Fisher* when applied to the technology of 1994 instead of the technology of 1949 clearly indicates that the claims of the present application are fully enabled by one of skill in the art .....in 1994. *Amgen* also applied the standard of *In re Fisher* and

discussed *In re Fisher* in a positive light, and assessed enablement of the claims at the time the applications in issue were filed, in 1983. This is eleven years before the present application was filed, and the techniques and knowledge of the skilled in the art have drastically changed during that time as discussed in the Appeal Brief. Again, to correctly apply *In re Fisher and Amgen*, the level of skill of those in the art must be determined ad og the time of the application. In 1997, the specification would have enabled one of ordinary skill in the art to make and use the compositions and molecules defined by the pending claims.

It is incorrect to argue that all of the *Forman* factors must be applied. The Examiner states, "Having established the breadth of the claims Wands now requires that one consider the number of working examples presented in the instant application." (page 18 of Examiner's answer). The Federal Circuit explicitly stated in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling" *Id.* at 1213. Thus, the specification does not require working examples to meet the correct legal standard of whether or not the required experimentation would be undue.

With respect to *Ex parte Mark* 12 USPQ2d 1904 (Bd. Pat. App. and Int., 1989) the Examiner's position that "in light of the working examples and guidance provided by that specification, [protein chemistry] was believed to be sufficiently predictable that this change could be made in any protein with a reasonable expectation that the modified protein would retain its original function" is incorrect. *Mark* does not use the language "sufficiently predictable." Mark states, "one skilled in the art would be able to routinely *determine* whether

deletion or replacement of the cysteine residues would result in a mutein which is within the claims on appeal." Id. at 1906 (emphasis added). The word "determine" as used in *Mark* includes using routine experimentation and is not limited to being able to predict *a priori* which molecules are or are not in the claims. In support of this, the Board is directed to page 1905 of *Mark* where the Board stated, "In support of the rejection, the Examiner relies . . . [on a statement in the specification which is] 'A transition at nucleotide 485 of the IFN-beta gene. The mutein lacked the biological activity of native IFN-beta leading the authors to conclude that the replaced cysteine was essential to activity.'" Id. at 1905. This conclusion was based on testing the molecule for activity, not predicting its activity.

The Claim to the Molecule Encoding Human SR-BI is Enabled.

Claim 19 is drawn to the molecule of claim 11 which encodes a human scavenger receptor BI molecule. The Examiner asserts this cannot be enabled because the cDNA sequence is not provided.

Note that there is no argument that one cannot obtain the claimed molecule using standard hybridization techniques based on SEQ ID Nos 3 and 7, using a human library. Rather the argument is a round about (and factually incorrect) argument that one must have the cDNA sequence of a molecule in order to produce the DNA. There is absolutely no scientific or legal basis for such an argument. Fifteen to twenty years ago it was routine to isolate the DNA encoding a molecule, put it into a vector and express the molecule. Isolation can be by hybridization, as claimed, using the reagents as described and claimed. This is not something

requiring undue experimentation, particularly in view of the abundance of data regarding activity and the DNA sequence from two totally different species that was described in the application as originally filed. All of the patents issued by the U.S. Patent Office based on deposit of a DNA molecule, which had not been sequenced at the time of filing the application, would be invalid were this the case. However, it has long been recognized that the standard is whether one can make and use what is claimed, without undue experimentation, not whether all possible embodiments are in hand as of the date of filing.

What distinguishes a human scavenger receptor BI encoding DNA is its source: human cells. As is readily apparent from a review of the sequences of the DNA molecules encoding mouse, hamster, and human scavenger receptor BI, these molecules are quite conserved, can be isolated by hybridization as claimed, have the same three dimensional structure shown in Figure 1B, and the same binding activity.

The claims are adequately described under the standard of Eli Lilly

Appellants are not in "complete conflict" with *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as asserted by the Examiner. Appellants have argued in the Appeal Brief that *Regents*, should be restricted to the specific fact situations that *Regents* presents because 1.the *Regents* decision itself indicates how important precedent on very similar fact situations was in their determination and 2. the *Regents* decision has not overruled other precedent dealing with the description issue because *Regents* was not an *en banc* decision. *Regents* stands for the proposition that when you have nothing more than the

words "cDNA of X" that this is not an adequate description of the structure of X because it is merely a label for X. This is not the situation in the present application because there are structural limitations on the present claims, structural limitations which were not present in the claims at issue in *Regents*.

Summary

In summary, one skilled in the art can determine whether a molecule, or method of use thereof, falls within the scope of the claims by:

determining if the nucleotide molecule hybridizes to SEQ ID Nos 3 and 7; and

encodes a protein which looks like a scavenger receptor BI protein and selectively binds to both low density lipoprotein and to actylated low density lipoprotein.

This is even more readily apparent from the dependent claims, which require the molecule to be expressed in certain cell types (adipocytes, lung cells and liver cells) (claim 12); hybridizing under stringent conditions to SEQ ID No. 3 (claim 13); and encoding a protein defined by the amino acid sequence of SEQ ID No. 4. The claims are therefore definite, and enabled, by the specification.

b. The Claims are definite under 35 U.S.C. §112, second paragraph

The Claims Define Method Steps

The claims were rejected on the basis that the claims fail to define method steps. This rejection ignores the claim language.

For example, claim 44 requires the following steps:

Providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein,

Adding the compound to be tested to the assay, and

Determining if the amount of modified low density lipoprotein or low density lipoprotein bound by the scavenger receptor protein is altered.

What more is required for one to know whether or not their actions fall within the scope of the claim? There is no requirement that each step be elaborated detailed – to do so would eviscerate the utility of the claimed method from excluding competition by those who have done nothing more than benefit from appellants' disclosure.

The Examiner states, "[claim 49] is drawn to a method of inhibiting the binding of a lipoprotein to a receptor protein but the claim recites no steps which would result in this inhibition, or any steps at all for that matter." (page 8 of the Examiner's Answer). This conclusion ignores the claim language, which is drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes, comprising:

Selectively inhibiting binding of lipoprotein to the scavenger receptor BI (basically as defined by claim 1) under conditions wherein low density lipoprotine is bound to the scavenger receptor.

Claims are interpreted in view of the specification, which provides numerous examples of compounds which bind to the scavenger receptor protein, competitively or non-competitively, as discussed above, as well as the conditions under which this binding occurs and how to assay for inhibition of binding. Therefore one skilled in the art can determine whether their actions fall within the scope of the claim. Nothing more definite is required.

There is some additional argument by the Examiner regarding enablement of the claimed methods for therapeutic applications which, to the extent it is relevant, is addressed more properly above under the first paragraph rejection, not definiteness.

One Skilled in the Art Can Determine if a Protein is an SR-BI Protein.

The rejections relating to the meaning of scavenger receptor protein have been addressed in the appeal brief and again in the section above relating to enablement.

The arguments relating to hybridization defy conventional understandings by those skilled in the art. One must use the proper perspective in determining the meaning of the claims. The correct analysis is not whether one can interpret the claims to encompass absurd embodiments but how one skilled in the art would interpret the claims. One skilled in the art is not going to conduct hybridizations under lax conditions. However, even if one did so, the

molecule must still encode a protein which has the requisite function – which simply is not going to occur except under fairly stringent conditions.

The argument regarding degenerate seems to imply that those skilled in the art know what "degenerate variants" are. If so, the claims certainly cannot be indefinite.

The remaining rejections seem to go to particular preferences by the Examiner which Appellant would certainly make if required but for the status of the prosecution and the other rejections.

c. Rejections under 35 U.S.C § 102

The Appellants were in possession of the hamster SR-B1 cDNA before the date of the Calvo et al publication, as established by the Declaration under 37 C.F.R. §1.131 of Monty Krieger and Susan Acton (and stipulated to by the Examiner, see page 14 of the Examiner's Answer). The Appellants did not state that the CD-36 and rat LIMP-II proteins were the same protein or the same family of proteins as the claimed SR-B1s, as asserted by the Examiner. The Appellants asserted that CD-36, Limp-II, and SR-B1 were in the same *superfamily* and that they provided a nexus to the molecules of the claimed genus. This was evidenced by the fact that Calvo et al. utilized members outside of the SR-B1 family, as a first step, to isolate Cla-1, namely CD-36 and Limp-II A, the very proteins identified in the database search provided in the 37 C.F.R. § 1.131 Declaration of Krieger and Acton.

A clarification of the technology that was used by Calvo et al. and is discussed in the Krieger and Acton Declaration is required. Calvo et al. cloned Cla-1 in the following manner.

First, Calvo et al. used degenerate primers from human CD-36 and Rat Limp-II to clone the human homologue of Limp-II out of a λgt11 library of human placenta DNA. Second, after obtaining a partial sequence of human Limp-II, Calvo et al. made another set of degenerate primers based on *human* Limp-II and screened a number of human cDNA libraries and obtained Cla-1.

Calvo et al. does not disclose any other SR-B1 proteins. Calvo et al. does not disclose a function for Cla-1, and in fact, indicate that it will be "difficult to envisage a function for Cla-1." (page 18934).

Appellants' have shown that they were in possession of the hamster SR-B1 cDNA before Calvo et al. disclosed Cla-1. Perhaps as importantly, Appellants' knew the function of the protein encoded by the cDNA, because they had expressed the cDNA in cells and conducted binding studies, thereby establishing the unique and surprising binding activities of the claimed protein.

Limp-II and CD-36 are members of the same protein *superfamily*, known as the CD-36 superfamily. The homology between rat Limp-II and human CD-36 was known well before the publication of Calvo et al., as evidenced by the fact that Calvo et al. cites Vega et al. for this proposition. (Vega et al., "Cloning, sequencing, and expression of a cDNA encoding rat LIMP II,

a novel 74-kDa lysosomal membrane protein related to the surface adhesion protein CD36" J. Biol. Chem. 1991 Sep 5;266(25):16818-24). Cla-1 is a member of the SR-B1 family (genus) of proteins as claimed in the present application. Thus, there exists a superfamily of proteins called CD-36 which has within it, a number of different families of proteins called for example, CD-36, Limp-II, and now SR-B1.

The Examiner's position is that the possession of the first member of the family of SR-B1, namely the hamster homologue, is not as pertinent as the information contained in the Calvo et al. publication with respect to the genus of SR-B1 proteins because Appellants' 1.131 Declaration allegedly did not contain information that the homologue of hamster SR-B1 would hybridize to the human SR-B1. The Examiner further asserts that it was not until Calvo et al. that information was provided that "Limp-II is conserved between rodents and humans." Whether Limp-II is shown to be conserved between humans and rodents is **only** necessary if you are going to use Limp-II, one family, to clone a member of another family, within the CD-36 superfamily. Appellants' **did not** require this information because they **already had** a member of the sought family, namely hamster SR-B1, which Calvo et al. did not have, and routinely set about establishing that one could (and they did) obtain the DNA from other species.

Appellants merely provided the sequence homology information in their possession prior to the date of Calvo et al. to show that Appellants were aware of the relationship between the hamster SR-B1 protein and the other family members of the CD-36 superfamily, not other

members of the family, SR-B1. The relationship between hamster SR-B1 and the other members of the genus, or family, of SR-B1, is defined by the hamster SR-B1 itself.

The case law for what must be shown in a 1.131 declaration is discussed in the Appeal Brief. In summary, the CCPA in *In re Tanczyn*, 347 F.2d 830, 146 USPQ 298 (CCPA 1965) has indicated that a declaration or affidavit must establish the prior possession of the whole invention claimed, when the rejection is under 35 U.S.C. § 103 and possession of only the disclosed subject matter when the rejection is based on 35 U.S.C § 102. In meeting the burden of showing possession the CCPA has held that facts showing a completion of the invention to the same extent as the invention is disclosed in the reference is sufficient, and that an exact showing of what is in the reference is not required to do this. *In re Wakefield,* 422 F.2d 897, 164 USPQ 636 (CCPA 1970) (*following In re Clarke* 356 F.2d 987, 148 USPQ 665 (CCPA 1966)). This is clearly analogous to the present rejection. The Appellants conceived and reduced to practice a member of the family of proteins called SR-B1 prior to the time Calvo et al. published a member of the family of proteins called SR-B1. Calvo et al. shows nothing more of relevance with respect to the claimed compositions than the sequence of a member of the family of proteins called SR-B1. In fact, Calvo et al., shows far less of what is determinative of the scope of the present claims, than the Krieger and Acton Declaration. Calvo et al., does not disclose the binding capabilities of the Cla-1 protein. In fact, Calvo et al. does not even know the *function* of the Cla-1 protein. The claims of the present application clearly require specific binding activities and specific functions for the molecules encompassed by the genus, functions which were

discussed and conceived of prior to the Calvo et al. publication. Thus, according to *Wakefield,* Appellants have clearly met their burden for showing possession of the claimed subject matter to the extent that the reference which they were antedating showed the claimed subject matter.

The CCPA stated in *In re Clarke*, "Claims do define 'the invention,' but in a given case may be of varying scope while still defining the same invention; what is 'the invention,' should not be confused with the scope thereof in this area of the law dealing with establishing prima facie a case of prior inventorship." Id. at 669. Thus, the question of what the invention defined by the claims of the present application is important. The "invention" was the isolation and possession of the first gene of a new CD-36 family, the SR-B1 receptors **and** the showing of a specific function that this new family possessed. Once this gene was isolated and a function of its encoded protein was known, it ***should be*** undisputed that it would have been obvious to one of ordinary skill in the art to obtain the remaining members of the claimed family of proteins, and that it would not have required one of skill in the art undue experimentation to do so. The Examiner's statement to the contrary, no evidence has been presented why Calvos' sequence should not have been obvious from appellants' sequence. With respect to the 1.131 Declaration submitted by the Appellants, these two aspects are "the invention" as envisioned by the *Clarke* court and fully disclosed by the Declaration.

d. Rejection Under 35 U.S.C. § 103

This rejection is moot because the Appellants have antedated this reference with the 1.131 Declaration of Krieger and Acton as discussed above. The Appellants were in complete

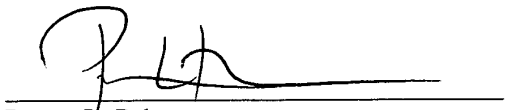
possession of the molecules of claims 21 and 22 as discussed in the 1.131 Declaration of Krieger and Acton. Claims 21 and 22 are drawn to expression vectors for SR-B1 proteins and cells harboring these expression vectors. As shown in the Krieger and Acton 1.131 Declaration Appellants had expressed the SR-B1 protein and had already assayed this protein for function. Calvo et al. had not yet expressed the Cla-1 at the time of the Calvo et al. publication and didi not know the function of Cla-1. The claims require function and the Declaration of Krieger and Acton indicates that they had conceived of the SR-B1 function prior to the publication of Calvo et al. Thus, under the standard for possession set forth in *In re Tanczyn* Appellants have completed antedated the Calvo et al. publication with respect to claims 21 and 22.

(2) SUMMARY AND CONCLUSION

In conclusion, claims 11-13, 15, 19-22, and 44-50 are enabled under 35 U.S.C. § 112, first paragraph, because the limitation of hybridization and specific lipoprotein binding limit the claimed molecules and in the present case variants of the claimed molecules are fully enabled. Claims 11, 13-15, 19-22, and 44-50 are not vague and indefinite under 35 U.S.C. § 112, second paragraph. Claims 11, 19, and 20 are novel under 35 U.S.C. § 102(a) over Calvo et al., *J. Biol. Chem.* 268(25) 18929-18935 (1993) and claims 19, 21, and 22 are not obvious under U.S.C § 103 over Calvo et al., *J. Biol. Chem.* 268(25) 18929-18935 (1993) because the Rule 1.131 Declaration presented by Drs. Krieger and Acton shows that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo et al.

Appellants earnestly solicit the allowance of claims 11-15, 19-22, and 44-50.

Respectfully submitted,



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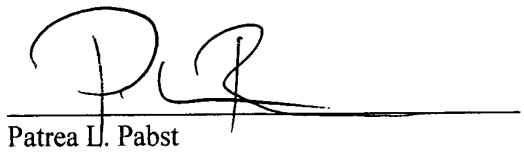

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Date: July 19, 1999